Future glycemic control of children diagnosed with type 1 diabetes mellitus at toddler and preschool/school age

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Abstract: Background The main objective of this study was to compare future glycemic control in children diagnosed with type 1 diabetes mellitus (T1DM) at toddler age and preschool/school age. In addition, we aimed to examine risk factors known to be associated with future glycated hemoglobin A1c (HbA1c) levels in children diagnosed with T1DM. Methods This is a retrospective cohort study of 85 patients diagnosed with T1DM at toddler age (group 1; 0-2.9 years; n = 36) or preschool/school age (group 2; 5-6.9 years; n = 49) who were followed up at the University Children's Hospital in Zurich for at least 10 consecutive years or until the age of 15 years. Results The mean HbA1c level in the first year after diagnosis had a highly predictive value about glycemic control in the following 6 years. In addition, a longer duration of T1DM was associated with higher HbA1c values. HbA1c values did not differ significantly within 11 years after diagnosis between children in the two age groups. Neither was a difference found when comparing the two groups in respect to their chronological age, although a trend was noted (p = 0.09). This trend is very likely due to a longer duration of diabetes in group 1. Conclusions HbA1c level in the first year predicts glycemic control for the next 6 years and deterioration of HbA1c values can be noted with longer duration of T1DM. Moreover, our study demonstrated similar future glycemic control in patients diagnosed with T1DM at toddler age and preschool/school age.

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Conclusions: HbA_{1c} level in the first year predicts glycemic control for the next 6 years and deterioration of HbA_{1c} values can be noted with longer duration of T1DM. Moreover, our study demonstrated similar future glycemic control in patients diagnosed with T1DM at toddler age and preschool/school age.

Keywords: diabetic ketoacidosis; HbA_{1c}; type 1 diabetes mellitus.

Introduction

Type 1 diabetes mellitus (T1DM) results from the autoimmune destruction of β-cells in the pancreas and the subsequent lack of insulin [1]. Despite advances in medical management, poor glycemic control in patients with T1DM is common and may lead to excess morbidity and premature mortality [2–4]. Therefore, tight glycemic control as assessed by the determination of glycated hemoglobin A_{1c} (HbA_{1c}) is essential and prevents future diabetic complications [5–7].

Several factors may influence future glycemic control or predict its future deterioration such as age at diagnosis, gender, socio-economic status, family structure, HbA_{1c} level during the first year after diagnosis, duration of diabetes or comorbidities [8]. In addition, the presence of diabetic ketoacidosis at diagnosis of T1DM has been established as risk factor predicting poor long-term glycemic control [9]. Moreover, there is evidence that children diagnosed with T1DM at an earlier age show better future glycemic control than when diagnosed later in life [2, 10, 11].

Recent studies reveal an increase in patients diagnosed with T1DM at an age <5 years [12–15], therefore playing an even more important role in clinical practice in the future.

Only a few studies exist to date [16] which further examine the glycemic control of children diagnosed at an age <5 years. In the aforementioned study, better glycemic control in children diagnosed at an age of 0–4 years for the following 5 years was observed. However, studies assessing long-term glycemic control are lacking. In the present study, we first aimed to examine risk factors that are known to be associated with future glycemic control. The main objective was to depict and compare long-term glycemic control in children diagnosed at an age of <3 years (toddlers) to preschool/school children (age 5–7 years).

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Materials and methods

Subjects

The study cohort included 89 children and adolescents diagnosed with T1DM at an age of either <3 (group 1) or between 5 and 7 years (group 2) who were treated at the University Children's Hospital in Zurich from 1990 to 2012. Diagnosis of T1DM was based on clinical features as well as the presence of islet auto-antibodies. Patients with monogenetic diabetes (n = 1), diabetes secondary to cystic fibrosis (n = 1) and children with syndromal diabetes (n = 2) were excluded. The main inclusion criteria were follow-up of at least 10 consecutive years at our institution and/or until an age of 15 years was reached. HbA_{1c} values of 10 patients (group 1: n = 6, group 2: n = 4) are missing in the first year, as T1DM in these patients was diagnosed elsewhere (other than our institution). The study was approved by the regional Ethics Committee of Zurich (number 2017-01752) and complies with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Study design

A retrospective cohort study was conducted at the Department of Pediatric Endocrinology and Diabetology, University Children's Hospital, Zurich, Switzerland. Patients were divided into two groups according to age at diagnosis: 0–3 years (toddlers, group 1) and 5.0–6.9 years (preschool/school children, group 2).

Analysis

Patient characteristics (age at diagnosis, educational level of parents, sex, comorbidities, pH at diagnosis, future insulin needs, form of insulin therapy, future HbA_{1c} levels) were extracted from medical records. Diabetic ketoacidosis (DKA) was defined as a pH at diagnosis of <7.30 and as blood glucose of >250 mg/dL, using the definition by Wolfsdorf et al. [17]. The form of insulin therapy was categorized in insulin pump use versus other. A random sample regarding insulin needs was extracted at least 10 years after diagnosis. The following comorbidities were extracted from patient records: hypothyroidism, celiac disease, cystic fibrosis and unknown syndrome.

Socioeconomic status (SES) score was calculated using a slightly modified version of Largo et al. [18]. In this score, the educational level of mother and father are added and their jobs are taken into account. Higher SES score values reflect lower levels of education.

Mean HbA_{1c} levels were measured at baseline and also at each visit at the clinic (every 3 months) initially using the DCA 2000+ Analyzer (Bayer/Siemens, Leverkusen/Munich, Germany), which was then replaced by the DCA Vantage Analyzer (Siemens, Munich, Germany). Mean HbA_{1c} level was calculated for each year and extracted until follow-up time of at least 10 years after diagnosis or an age of 15 years was reached.

Statistical analysis

Statistical analysis was conducted using SPSS 24 (IBM Corp; Statistics, New York, NY, USA). The level of significance was set to $\alpha = 0.05$. To examine the influence of sex, age at diagnosis, pH at diagnosis, SES score and insulin pump use on future HbA_{1c} levels, multiple regression analysis was conducted. Associations between HbA_{1c} levels during the first year and the following years were analyzed using partial correlations. To compare the different groups, t tests for independent samples and repeated measures analyses of variance (ANOVA) were calculated.

Additionally, potential covariates and confounders (sex, age at diagnosis, pH, duration of diabetes and SES score) were included in the analysis.

Results

In total, 85 patients with T1DM were included in the study: 36 children in group 1 (0–2.9 years; toddlers) and 49 in group 2 (5.0–6.9 years; preschool/school children). Baseline characteristics of the two groups are reported in Table 1. Demographic and clinical characteristics did not differ between the groups except for age at diagnosis ($p < 0.001$).

Commonly known predictors for future glycemic control such as sex, age at diagnosis, pH at diagnosis and SES-score did not have any influence on future HbA_{1c} levels in our study population (data not shown). Among others, the presence or absence of DKA at diagnosis did not influence future glycemic control, neither in the whole population (Figure 1) nor when analyzed within the two age groups (data not shown). Of note, mean HbA_{1c} level during the first year had a significant influence on future glycemic control during the following 6 years as shown for the second ($p < 0.001$; Figure 2A) and the sixth year ($p < 0.001$; Figure 2B). Furthermore, longer duration of T1DM was significantly associated with higher HbA_{1c} values ($p < 0.001$; Figure 3A and B).

Long-term glycemic control did not differ significantly between the two age groups over an observation period of 11 years after the diagnosis of T1DM (Figure 3A). Similarly, HbA_{1c} levels did not differ between the two age groups for a given chronological age, although a trend was noted ($p = 0.09$; Figure 3B) towards lower HbA_{1c} levels in the later diagnosed group 2.

Discussion

Several factors influence future glycemic control in children and adolescence with T1DM [8, 9]. The present study aimed to examine whether an early age at diagnosis of T1DM impacts on future glycemic control. Children diagnosed with T1DM at toddler age and preschool/school age showed similar glycemic control with respect to years after diagnosis and to chronological age.

Table 1: Baseline characteristics of the study population.

	Age at diagnosis		p-Value
	Toddlers 0–2.9 years	Preschool/school children 5–6.9 years	
Number of patients	36	49	
Age at diagnosis, years	2.07 ± 0.10	6.11 ± 0.07	<0.001
Sex			
Female	18 (50%)	22 (45%)	0.64
Male	18 (50%)	27 (55%)	
pH at diagnosis	7.25 ± 0.02	7.31 ± 0.02	0.11
Socioeconomic status score[a]	5.27 ± 0.25	5.21 ± 0.25	0.86
HbA_{1c}-value 1st year	7.34 ± 0.14	7.26 ± 0.11	0.65
Insulin needs, IU/kg body weight	0.95 ± 0.05	1.01 ± 0.06	0.44
Form of therapy insulin pump	3	3	0.82
Comorbidities			
Celiac disease	5	3	0.23
Hypothyroidism	1	2	0.75

Continuous variables are presented as mean ± SEM, categorical variables in n (%). [a]Socioeconomic status score ranging from 2 to 12 (2 being the highest socioeconomic status).

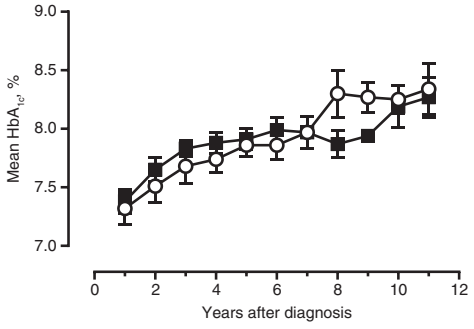

Figure 1: The presence of DKA at the time of diagnosis does not impact on future glycemic control.
Mean HbA_{1c} levels of the two age groups are plotted in relation to diabetes duration. Non-DKA (○, n = 49), DKA (■, n = 25).

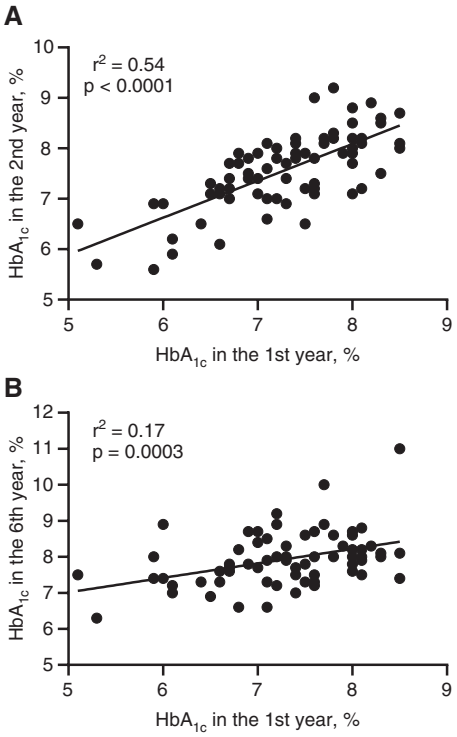

Figure 2: HbA_{1c} value in the first year predicts future HbA_{1c} values.
Correlation between mean HbA_{1c} value in the first year after diagnosis and mean HbA_{1c} values in the second (A, $p < 0.0001$; n = 75) or mean HbA_{1c} values in the sixth (B, $p = 0.0003$; n = 75) year is depicted.

Several variables which are known predictors of future glycemic control [8, 10, 11, 16], such as sex, age at diagnosis and SES score were not significant predictors of future HbA_{1c} levels in our study population. These results may suggest that our study did not have a large enough sample size to investigate these effects. Recently, the presence of DKA at diagnosis of T1DM was reported to predict poorer long-term glycemic control [9]. In contrast, we did not find any significant difference of future HbA_{1c} levels dependent on the presence or absence of DKA. Compared to our study, older children and adolescents were included in the former, which may account for the observed difference. Of note, the mean HbA_{1c} level in the first year had a highly predictive value for glycemic control in the following 6 years. This is in concordance with previous studies [19] and emphasizes the importance of achieving the target HbA_{1c} as early as possible, also in order to prevent future diabetic complications [6, 7]. In addition, patients who will have poorer future glycemic control can be targeted

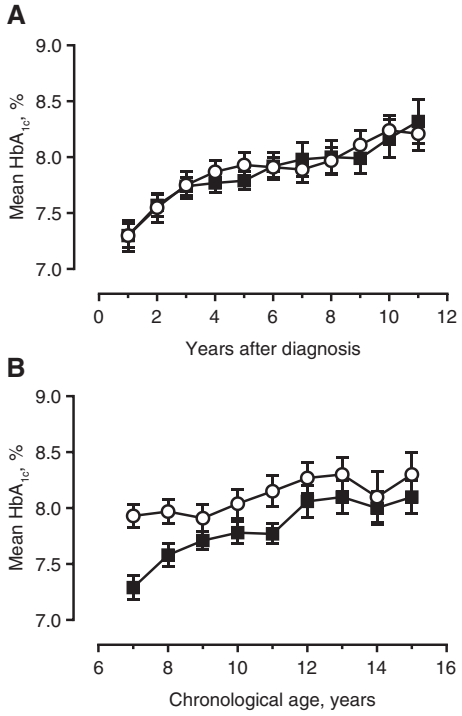

Figure 3: Age at diagnosis does not predict future glycemic control. Mean HbA_{1c} levels of the two age groups are plotted in relation to diabetes duration (A, group 1 (○) n = 30–36; group 2 (■) n = 45–49) or to chronological age (B, group 1 (○) n = 26–36; group 2 (■) n = 45–47).

earlier and additional support to these patients can be granted.

As reported previously [20], deterioration of glycemic control with longer diabetes duration was noted in our study. We observed such deterioration especially during puberty and adolescence, a time period that is characterized by accelerated growth due to increased growth hormone release inducing insulin resistance as well as hormonal and psychological/social changes, which may negatively impact on insulin regimen adherence [21, 22].

Only a few studies have so far examined and compared glycemic control in children diagnosed with T1DM in the first years of life. Most of these studies compared younger (e.g. diagnosis of T1DM at 0–5 years of age) with older (6–12 years) age groups [2, 8] and have not focused on the comparison of children aged <7 years. Herein, we did not find a significant difference of the two different age groups regarding long-term glycemic control, i.e. children diagnosed with T1DM at toddler age showed similar HbA_{1c} levels compared to children diagnosed at an age between 5 and 7 years. Indeed, no difference in mean HbA_{1c} values between the two age groups were found up to 11 years after the diagnosis of T1DM. Neither was a difference found when comparing the two groups in respect to their chronological age, although a trend was noted (p = 0.09). This trend is very likely due to the longer duration of diabetes in group 1 (diagnosed at toddler age).

It is believed, that first childhood memories occur between the age of 3–4 years, although there is a great variability (13). One could argue that a missing memory of a life without diabetes may positively influence future HbA_{1c} levels. This may imply that patients enrolled in group 1 (toddlers) may not yet possess memories of a life without diabetes, whereas children included in group 2 (preschool/school children) do. As we found no statistically significant difference in future glycemic control between the two groups, this may indicate that the memory of a life without diabetes does not have an influence on future HbA_{1c} levels. However, prospective studies are needed to prove a possible correlation and to take each patient's onset of first childhood memories into account.

This study has inherent limitations and strengths. The strength of this study is the long observation period (at least 10 consecutive years). In addition, all children were treated by the same staff of a single diabetes center and, thus, received a similar insulin injection regimen during the observed time period (from 1990 to 2012). However, insulin analogs such as insulin aspart and insulin detemir as well as continuous subcutaneous insulin infusion therapy by an insulin pump (n = 6 patients) were introduced over time. Of note, insulin pump therapy was more commonly applied in children of the youngest age group, however, such difference reached no statistical significance. The retrospective study design is clearly a weakness of the present study.

In conclusion, mean HbA_{1c} level in the first year after T1DM diagnosis predicts glycemic control for the next 6 years and deterioration of HbA_{1c} values can be noted with longer duration of T1DM. Moreover, our study demonstrates similar future glycemic control in patients diagnosed with T1DM at toddler age (0–3 years) and preschool/school age (5–6.9 years).

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